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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 01/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/025,222	PELLETIER ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-104* is/are pending in the application.

4a) Of the above claim(s) *48-65,73-83 and 92-104* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66-72 and 84-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

[1] Claims 48-104 are pending in the application.

Election/Restriction

[2] Applicants' election with traverse of Group I, claims 66-72 and 84-91, filed October 06, 2003, is acknowledged. Because applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

[3] Claims 48-65, 73-83 and 92-104 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Specification/Informalities

[4] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested:

[5] The attempt to incorporate subject matter into this application by reference to a hyperlink embedded in the specification (see for example, page 101, line 25) is improper. Incorporation of subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an

improper incorporation by reference. See MPEP 608.01 regarding hyperlinks in the specification and 608.01(p), paragraph I regarding incorporation by reference.

Claim Objections

[6] Claim(s) 67 and 68 are objected to because of the following informalities: the terms "an biological" in claim 67 and "for bacteriophage" in claim 68, are grammatically incorrect and should be replaced with, for example, "a biological", "from bacteriophage", respectively. Appropriate correction is required.

[7] Claims 66-67 are objected to in the recitation of "*S. aureus*". In order to clarify the meaning of the terms, it is suggested that applicants amend the claim to recite the term for which the abbreviation represents, i.e., *Staphylococcus aureus*", at least once in the claims.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

[8] Claims 66-71 and 81-91 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to (in relevant part) an enriched bacterial polypeptide. It is noted that a definition for the term "enriched" is disclosed as page 32, lines 22-29 of the specification. However, there is no indication that this term is meant to indicate the hand of the inventor as the definition

clearly states, "[s]uch polypeptides may be natural". It is suggested that applicants amend the claim to remove the term "enriched". See MPEP § 2105.

[9] Claim 72 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim is drawn to a composition comprising a first and second polypeptide domains. The claim reads on a product of nature and should be amended to indicate the hand of the inventor, e.g., by insertion of "purified" or "isolated". See MPEP § 2105.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[10] Claim(s) 66-71 and 84-91 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[11] Claims 66-71 and 84-91 are indefinite in the meaning of the term "enriched". While it is acknowledged that the specification provides a definition for the meaning of the term (page 32), it is unclear from this definition as to the meaning of the term. It is suggested that applicant(s) clarify the meaning of the claim(s).

[12] Claim 91 is indefinite in the recitation of "biologically active". The specification discloses the meaning of this term at pages 21-26 of the specification. However, the scope of activities encompassed by this "definition" is vague and it is unclear from the definition of this term what functions of the claimed polypeptide applicants intend as the

meaning of "biologically-active". It is suggested that the term "biologically-active" be replaced with a term that clearly defines applicants' intended biological function.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[13] Claims 66-72, 84-87, and 89-91 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 66-71 are drawn to a genus of bacterial polypeptide fragments or variants of a polypeptide comprising SEQ ID NO:2 having the ability to bind a bacteriophage polypeptide. Claim 72 is drawn to a composition comprising a genus of polypeptide domains, wherein the first polypeptide domain is derived from a STAAU_R9 polypeptide comprising SEQ ID NO:2 and the second domain is derived from a bacteriophage polypeptide binding to said STAAU_R9 polypeptide. Claims 84-87 and 89-91 are drawn to polypeptides or primases comprising fragments and variants of SEQ ID NO:2.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a

representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the genera of recited polypeptides is widely variant in both structure and function and the single disclosed species of polypeptides as encompassed by the claims, *i.e.,* SEQ ID NO:2 fails to represent all species encompassed by the claimed genera, which encompasses a vast number of proteins, which are structurally and functionally diverse. The specification fails to describe any additional representative species of the claimed genus. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". Given the lack of description of a representative number of polypeptides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[14] Claims 66-72, 84-87, and 89-91 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the isolated polypeptide of SEQ ID NO:2, does not reasonably provide enablement for *all* bacterial polypeptide fragments or variants of a polypeptide comprising SEQ ID NO:2 having the ability to bind a bacteriophage polypeptide; *all* compositions comprising *any* first polypeptide domain derived from a STAAU_R9 polypeptide comprising SEQ ID NO:2 and *any* second domain derived from a bacteriophage polypeptide binding to said STAAU_R9 polypeptide; or *all* polypeptides or primases comprising fragments and variants of SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: The claims are so broad as to encompass *all* bacterial polypeptide fragments or variants of a polypeptide comprising SEQ ID NO:2 having the ability to bind a bacteriophage polypeptide; *all* compositions comprising *any* first polypeptide domain derived from a STAAU_R9 polypeptide comprising SEQ ID NO:2 and *any* second domain derived from a bacteriophage polypeptide binding to said STAAU_R9 polypeptide; and *all* polypeptides or primases comprising fragments and variants of SEQ ID NO:2. The broad scope of the claimed polypeptides is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims. In this case the disclosure is limited to the isolated polypeptide of SEQ ID NO:2.

- The lack of guidance and working examples: The claims encompass a vast number of derivatives and mutants of SEQ ID NO:2. The specification provides only a single working example of the recited polypeptides, *i.e.,* SEQ ID NO:2 and fails to provide guidance for isolating the entire scope of claimed or recited polypeptides as broadly encompassed by the claims. a method for isolating the polypeptide and encoding nucleic acid of SEQ ID NO:2. This single working example fails to provide the necessary guidance for making and/or using the entire scope of recited polypeptides. The specification fails to provide guidance regarding those nucleotides of SEQ ID NO:1 or amino acids of SEQ ID NO:2 that may be altered by substitution, addition, insertion, and/or deletion with an expectation of maintaining the desired activity. Furthermore, the specification fails to provide guidance as to how to use those variant polypeptides – both naturally and non-naturally occurring - that encode polypeptides having activities

other than the desired activity, *e.g.,* non-functional polypeptides or polypeptides having activity other than SEQ ID NO:2.

- The high degree of unpredictability in the art: The nucleotide sequence of an encoding nucleic acid determines the corresponding encoded protein's structural and functional properties. Predictability of which changes can be tolerated in an encoded protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within an encoding nucleic acid's sequence where modifications can be made with a reasonable expectation of success in obtaining an encoded polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. In this case, the necessary guidance has not been provided in the specification as explained in detail above. Thus, a skilled artisan would recognize the high degree of unpredictability associated with making and using the entire scope of recited polypeptides.

- The state of the prior art supports the high degree of unpredictability: The state of the art provides evidence for the high degree of unpredictability in altering a polynucleotide/polypeptide sequence with an expectation that the encoded polypeptide will maintain the desired activity/utility. For example, Branden et al. ("Introduction to

Protein Structure", Garland Publishing Inc., New York, 1991) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). While it is acknowledged that this reference was published in 1991, to date there remains no certain method for reasonably predicting the effects of even a *single* amino acid mutation on a protein. Such mutations may even completely alter a protein's activity. As a representative example, Witkowski et al. (*Biochemistry* 38:11643-11650) teaches that a single amino acid substitution results in conversion of the parent polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see e.g., Table 1, page 11647). Thus, the prior art acknowledges the unpredictability of altering a protein-encoding sequence with an expectation of obtaining a protein having a desired function and discloses that even a single substitution in a polypeptide's amino acid sequence may completely alter the function of a polypeptide.

- The amount of experimentation required is undue: While methods of generating variants and mutants of a given polypeptide, *e.g.,* by site-directed mutagenesis, are known, it is not routine in the art to screen for *all* polypeptides having a substantial number of substitutions or modifications, as encompassed by the instant claims. Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as

evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use
> or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

[15] Claim(s) 66-71, 87, and 91 are rejected under 35 U.S.C. 102(b) as being anticipated by O'Donnell et al. (WO 99/37661; cited in the IDS filed July 07, 2003 as reference A7). Claims 66-71 and 87 are drawn to polypeptide fragments or variants of SEQ ID NO:2 and optionally having the ability to bind a bacteriophage polypeptide. O'Donnell et al. teach a polypeptide encoded by *S. aureus dnaG* (pages 33-34).

O'Donnell et al. teach *dnaG* encodes a polypeptide having primase activity (page 3). The polypeptide of O'Donnell et al. is 93.5 % identical to SEQ ID NO:2 and is 98.1 % similar to SEQ ID NO:2 (see attached sequence alignment). This anticipates claims 66-71 and 87.

[16] Claim(s) 84 and 89-91 are rejected under 35 U.S.C. 102(e) as being anticipated by Doucette-Stamm et al. (US Patent 6,380,370). Claims 84 and 89-91 are drawn to polypeptide variants of SEQ ID NO:2. Doucette-Stamm et al. teach a polypeptide comprising an amino acid sequence that is 94% identical to amino acids 1-50 of SEQ ID NO:2 and comprises at least 10 contiguous amino acids of amino acids 1-34 of SEQ ID NO:2. This anticipates claims 84 and 89-91.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[17] Claim(s) 66-71, 84-85, 87, and 89-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Benton et al. (US Patent 6,037,123; cited as IDS reference A1 in the IDS filed July 07, 2003) in view of Burgett et al. (US Patent 6,162,617) and Harbarth et al. (*Arch Intern Med* 158:182-189; cited as reference A20 in the IDS filed December 23, 2002). The claims are drawn to variants of SEQ ID NO:2 optionally having the ability to bind a bacteriophage polypeptide.

Benton et al. teach a nucleic acid isolated from *S. aureus* encoding a polypeptide that has strong similarity to the dnaG genes of *L. monocytogenes, L. lactis, B. subtilis, and E. coli* encoding DNA primase (columns 89-93). The polypeptide encoded by the nucleic acid of Benton et al. is 100% identical to amino acids 1-50 and 561-599 of SEQ ID NO:2 and shares 93.25% similarity to SEQ ID NO:2. Benton et al. teach methods for evaluating their gene as a therapeutic target (columns 241-243). Benton et al. do not teach a polypeptide encoded by their nucleic acid.

Burgett et al. disclose, "[w]idespread resistance in common pathogenic bacterial species has justifiably alarmed the medical and research communities. Frequently, resistant organisms are co-resistant to several antibacterial agents. Penicillin resistance in Streptococcus pneumoniae has been particularly problematic. This organism causes upper respiratory tract infections. Modification of a penicillin-binding protein (PBP) underlies resistance to penicillin in the majority of cases. Combating resistance to agents will require research into the molecular biology of pathogenic organisms. The goal of such research will be to identify new antibacterial agents" (column 1). Burgett et al. teach cloning of the dnaG gene of *Streptococcus pneumoniae* and teach expressing the protein encoded by the dnaG gene for screening novel antibiotics (columns 7-8).

At the time of the invention, *S. aureus* was known to cause bacterial infections in the human population. For example, Harbarth et al. teach, "[m]ethicillin-resistant Staphyloeoceus aureus (MRSA) has become a worldwide problem, adding to the overall burden of nosocomial infections" (page 182, introduction).

Therefore, it would have been obvious to one of ordinary skill in the art to express the protein encoded by the nucleic acid of Benton et al. One would have been motivated to express the protein encoded by the nucleic acid of Benton et al. in order to determine if the encoded protein is a DNA primase as suggested by Benton et al. and to use the protein to screen for novel antibiotics because of the teachings of Burgett et al. and Harbarth et al. as described above. One would have a reasonable expectation of success for expressing the protein of Benton et al. because of the results of Benton et al. Therefore, claims 66-71, 84-85, 87, and 89-91, drawn to polypeptide variants of SEQ ID NO:2 would have been obvious to one of ordinary skill in the art.

[18] It is noted that O'Donnell et al., Doucette-Stamm et al., and Benton et al. do not disclose that their respective polypeptide or polypeptide encoded by their nucleic acid has the ability to bind to the polypeptide of SEQ ID NO:4. However, absent evidence to the contrary, this is an inherent property of the polypeptide of O'Donnell et al. and Doucette-Stamm et al. and the polypeptide encoded by Benton et al. Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

Conclusion

[19] Status of the claims:

- Claims 48-104 are pending.
- Claims 48-65, 73-83 and 92-104 are withdrawn from consideration.
- Claims 66-72 and 84-91 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652

12-23-03

DAVID STEADMAN
PATENT EXAMINER